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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,071	08/17/2006	Michel Cuenod	33588-US-PCT	1693

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ONE HEALTH PLAZA 101/2
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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,071	CUENOD ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58,85-101 and 121-147* is/are pending in the application.

4a) Of the above claim(s) *4,9-39,43-58,85-101 and 121-147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I and the election of GCL in the reply filed on 9/23/2010 are acknowledged.

2. Claims 1-58, 85-101, 121-147 are pending. Claims 59-84, 102-120, 148-188 are cancelled.

3. Claims 4, 9-39, 43-58, 85-101 and 121-147 are withdrawn as being drawn to a nonelected invention.

4. An action on the merits for Claims 1-3, 5-8, and 40-42 is set forth below.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 6/25/2010 has been considered by the examiner.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-3, 5-7, and 41-42 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed towards diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular glutathione level.

Based upon consideration of all of the relevant factors with respect to the claims as a whole, claims 1-3, 5-7, and 41-42 are held to claim an abstract idea, and are therefore rejected as ineligible subject matter under 35 U.S.C. 101. The rationale for this finding is explained below:

The unpatentability of abstract ideas was confirmed by the U.S. Supreme court in *Bilski v. Kappos*, No. 08-964, 2010 WL 2555192 (June 28, 2010). Factors weighing toward patent eligibility include: (i) a recitation of a machine or transformation wherein the machine or transformation is particular, the machine or transformation meaningfully limits the execution of the steps, the machine implements the claimed steps, the article being transformed is particular, the article undergoes a change in state or thing (e.g., objectively different function or use), the article being transformed is an object or substance; (ii) a claim directed to applying a law of nature, wherein the law of nature is practically applied and the application meaningfully limits the execution of the steps; and (iii) the claim is more than a mere statement of a concept, such that the claim describes a particular solution to a problem to be resolved, implements a concept in some tangible way, and the performance of steps is observable and verifiable.

Reviewing each of the factors identified in the Fed. Register, Vol. 75, No. 143, page 43925-43926, the claims as a whole fail to meet the elements required for patent eligibility.

These claims are directed to methods requiring only the active step of determining. The specification is silent with respect to a particular definition or requirement for detecting. Broadly, detecting encompasses merely inspecting a

medical report or print out.

First, the claims do not involve a machine nor are executed by a particular machine. Thus, this factor weighs in favor of lack of patent-eligibility.

Second, the claims do not appear to require a transformation of a particular article. The claims merely are directed to “determining the presence or absence." As discussed above the specification fails to provide any definition for determining. The claims do not require any particular article is transformed or a transformation that changes the state of an article to have a different function or use. As such, the lack of a transformation of a particular article weighs in favor of lack of patent-eligibility.

Finally, the last factor also weighs in favor of lack of patent eligibility since a general concept is involved in executing the steps of the method. The claims are not limited to any particular concepts for executing the method. The claims effectively cover all possible methods for determining the presence or absence of at least one polymorphism, not only nucleic acid methods, but also merely looking at a database.

In sum, when the instant claims are considered as a whole, all factors relevant to the instant claims weigh in favor of a lack of patent-eligibility. Thus, the instant claims are claiming an abstract idea by covering a general concept and are not limited to a particular practical application of the concept.

Claim Rejections - 35 USC § 112/Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 5-8, and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method of determining an increased risk of schizophrenia in a human patient comprising obtaining a nucleic acid sample from a skin biopsy or blood of the patient and determining an decreased expression level of GCLM or GSH in the nucleic acid sample as compared to a control wherein an decreased expression level indicates and increased risk of schizophrenia, does not reasonably provide enablement for diagnosis of any mental disorder in any subject by detecting any level of expression of any gene involved in regulating the intracellular glutathione level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The breadth of the claims

The claims are drawn to diagnosing any mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular GSH

level including GLCM. As such the claims are drawn to diagnosis of any mental disorder in any subject by determination of any level of expression of at least one gene involved in regulating the intracellular GSH level including GLCM.

As discussed below, although the specification is enabling for the specific scope of a particular gene's expression level with a particular mental disorder in humans, however, the specification does not provide guidance for the breadth of the claims. Specifically the specification does not provide guidance for the breadth of the claims. Further, the art discloses that such associations are species, diseases, and genotype specific. As such, the associations made in one particular correlation would not be predictive in for any other correlation.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification and working examples

The specification asserts identification of genes that are expressed at lower levels in a subject affected by mental disorder such as schizophrenia (p. 12 lines 17-20). However, the claims are drawn to the determination of any level of expression, wherein in the instant specification the correlation is towards lower levels.

The specification asserts that the mental disorders include schizophrenic disorders, affective disorders, bipolar disorder, mood disorder, conduct disorder,

psychoactive substance use disorder, personality disorders, delirium, dementia, epilepsy, panic, ocd, intermittent explosive disorder, impulse control disorder, psychosis, ADHD, and manic or psychotic depression (p 12 lines 21-32). The specification provides a long list of disorders which are encompassed by the claims (p. 30-31). However, the specification only provides an example of one disorder. The art, as discussed below, teaches that associations in one type of mental disorder does not provide a predictably extrapolation to any other mental disorder.

The claims are towards any GSH level and the specification asserts that this can include GCL, GCLM, GSS, GPX, glutamate/cysteine exchange transporter (p. 13 1st paragraph). The specification has not provided guidance that any gene that alters GSH level is associated with mental disorder. Rather, the specification has provided a particular statistically significant correlation between one type of gene and a particular disorder. As the art teaches, below, these correlations are population and disease specific and must be individually examined. A correlation with regard to expression in one gene does not necessarily provide a direct correlation to any other gene.

The specification asserts that the biological sample may be obtained from a human or an animal (p. 16 lines 19-25). However, the specification only provides teachings of human sequences and samples. As shown by the art discussed below there is unpredictability with regard to comparing results from gene expression analysis data in human to other closely related animals.

The examples provide the expression genes taken from skin biopsies of patients (p. 62). Table 6 provides the expression levels of GCLM in cultures from schizophrenic

patients (p. 63). Example 2 looked at the GSH levels in blood and found lower GSH levels (p. 65). Although there appears to be a correlation between GCLM decreased expression and increased risk of Schizophrenia, this correlation does not provide guidance for the correlation of any other mental disease to expression. Furthermore, the claims are drawn to diagnosis. However, the specification has not provided that only patients with schizophrenia have lower levels of GSH and therefore the specification has not provided guidance for the diagnosis patients based only on the gene levels.

The unpredictability of the art and the state of the prior art

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Because the claims encompass any subject, whereas the instant specification provides only teachings of human sequences and samples, it is relevant to point out that there is a large amount of unpredictability with regard to comparing results from gene expression analysis data in humans to other even closely related animals. Enard et al (Science. 2002. April 12; 296(5566):340-43) teaches that large numbers of quantitative changes in gene expression can be detected between closely related mammals (p.342, middle col., last paragraph). Thus it is not predictable that the predictive lowered expression a gene from humans would be predictive in any other animal.

The state of the art teaches that there is a natural variation in gene expression among different individuals and the difficulty in applying gene expression results. The

art of Cheung et al (Nature Genetics 2003 Vol. 33 p. 422) teaches that there is natural variation in gene expression among different individuals. Cheung et al teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology 2001 Vol. 195 p. 53). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology 2001 Vol. 8 p. 37) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to

validation (p.38, third full paragraph).

The art of Cobb et al (Crit Care Med 2002 Vol. 30 p. 2711) teaches the unpredictability in analysis of gene expression in spleen and liver sample from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., lns.2-8). As such the art teaches that expression levels of the same nucleic acids in different tissue samples differ. Therefore the art indicates that an association of expression level to a disease in one sample would not be correlative to an association to any other sample type. Therefore the art suggests the unpredictability of associating expression levels in one particular sample type as compared to another. Herein in the instant case, the specification has shown support of using skin biopsy and blood, but has not shown to support for other sample types.

Although Cuenod et al. (WO 00/75668 A2 December 14, 2000 cited on IDS 6/25/2010) provides support for the association of GSH decreased expression and schizophrenia, this does not provide support the association in any gene involved in regulating GSH or any mental disorder. Tosic et al. (The American Journal of Human Genetics September 2006 Vol 79 p. 586) teaches that of the 14 genes studied that are involved in GSH metabolism two showed significant differences (GCLM and GSS) (p. 586 1st column 2nd paragraph and last paragraph). Therefore the art does not provide support that nay gene involved with GSH will have the same associations to schizophrenia. Further, Kishi et al. (ANN NY Acad Sci 2008 Vol 1139 p. 63) teaches

that there is no association between METH-induced psychosis and GCLM (p. 65 last paragraph). As such the art teaches that these associations between GSH genes and mental disorders must be individually examined for associations.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation and Conclusion

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. The claims are drawn to associations of diagnosis of mental diseases by the detection of any level of expression of any GSH related gene in any subject. Therefore the claims encompass analysis of a large number of mental disorders, expression levels and genes.

To practice the invention as broadly as it is claimed, the skilled artisan would have to determine associations in various species and determination of associations of any expression levels in a large number of mental disorders.

The skilled artisan would need to perform undue experimentation to determine such an association. Even if the extensive experimentation was performed, there is no assurance that any other additional genes, in any of these species, would be found to be associated with any mental disorders. Such random, trial by error experimentation is considered to be undue and highly unpredictable.

Further, the art indicates that these experimentations do not have a guarantee of success. Specifically both Kishi and Tosic et al. teach that these associations are disease and gene specific.

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the

claimed method.

Therefore the method as claimed would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 5-6, 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Cueno et al. (WO 00/75668 A2 December 14, 2000). Cueno et al was cited on the IDS filed 6/25/2010.

With regard to Claim 1, Cueno et al. teaches that GSH (e.g. a gene involved in regulating GSH level) has decrease expression level in schizophrenic patients (e.g. mental disorders) (p. 2 3rd paragraph).

With regard to Claim 5, Cueno et al. teaches that the level of GSH is significantly decreased by about 27% (p. 1 4th paragraph).

With regard to Claim 6, Cueno et al. teaches the identification of transcription of GSH (p. 3 last paragraph).

With regard to Claim 40, Cueno et al. teaches that the measurement was performed in samples and as such it would be considered ex vivo (p. 2 last paragraph).

With regard to Claims 41-42, Cueno et al. teaches that GSH (e.g. a gene involved in regulating GSH level) has decrease expression level in schizophrenic patients (e.g. mental disorders) (p. 2 3rd paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cueno et al. (WO 00/75668 A2 December 14, 2000) in view of Zong et al. (Free Radical Biology and Medicine 199 Vol 27 p. 1334).

Cueno et al. teaches that GSH (e.g. a gene involved in regulating GSH level) has decrease expression level in schizophrenic patients (e.g. mental disorders) (p. 2 3rd paragraph).

However, Cueno et al. does not teach measuring the nucleic acid using PCR.

With regard to Claims 7-8, Zong et al. teaches that expression levels of genes related to GSH can be performed with real time PCR (p. 1341 1st column last paragraph and p. 1339 last paragraph). As such Zong et al. teaches that expression can be determined using real time PCR.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Cueno et al. to detect expression level changes using real time PCR. Zong et al. teaches that real time PCR can be used to measure expression level changes. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure expression with RT-PCR with a predictable expectation of successful measurement as Zong et al teaches that this assay can be used to determine expression of genes involved in GSH regulation.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634